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PROVISIONAL UTILITY PATENT

APPLICATION
FOR
UNITED STATES LETTERS PATENT

TO ALL WHOM IT MAY CONCERN

Be it known we,

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have invented new and useful improvements in

Systems and Methods for Bioluminescent Computed Tomographic Reconstruction

for which the following is a specification.

Exhibit C

Systems and Methods for Bioluminescent Computed Tomographic Reconstruction

BACKGROUND

This invention relates to systems and methods for detecting a light-emitting source distribution in three dimensions as well as systems and methods for reconstructing an image from the detected signals from the source distribution based on data from a tomographic imaging modality, including but not limited to computed tomography (CT) or micro-CT .

Bioluminescent imaging techniques are currently known in the art. However, current imaging techniques are limited to the projective imaging mode. Therefore, three-dimensional structures and localization of light source cannot be resolved.

It is therefore desirable to combine an x-ray CT or micro-CT system with a light-emitting source CT system to perform bioluminescent computed tomography (BLCT). By combining a system for detecting light emission for multiple angles of view simultaneously with an imaging modality which allows the evaluation of two and three dimensional structural information, such as micro x-ray CT, the anatomic and/or structural details gained from the micro x-ray CT can be used to estimate the distribution of light scattering structures for purposes of directing the computed tomographic calculations required to create BLCT-based cross-sectional images. Such a system would enable, as non-limiting examples, both the calculation of the computed tomograms of chemo- luminescence, and the linking of the computed tomograms of chemo-luminescence to the highly detailed anatomic image sets derived from the x-ray CT imaging. In some embodiments, the tomographic reconstruction of bioluminescence can provide important added detail regarding regional location of reporter gene activity. By knowing the location of reporter gene activity and having micro-resolution images of anatomy, a user can follow the link between gene activation and pathologic processes.

SUMMARY

The present invention is directed to multi-modal imaging systems and methods. The present invention can reconstruct an image volume in a first tomographic modality,

map optical properties onto this volume from a database, and perform tomographic reconstruction in another modality based on the known optical properties. One preferred embodiment of the system can use bioluminescent CT and micro-CT combinations, but other system configurations are possible. Some embodiments can include an MRI scanner or micro-MRI scanner in conjunction with a fluorescent tomographic scanner. The imaging techniques and algorithms disclosed herein are exemplary only and other methods of combining data from multiple tomographic scanners can be used.

Some embodiments of the system can be capable of various resolutions depending on scanning times, possess extremely high photon detection sensitivity for mapping gene expression, and/or embody hardware and/or software technology for image reconstruction, registration, and analysis. Some embodiments can have the advantage of being configured to rapidly collect data with a higher signal-to-noise ratio. One preferred embodiment of the present invention can render bioluminescent imaging in a three-dimensional tomographic modality. In embodiments directed to bioluminescence, emitted photons can be collected from multiple three-dimensional directions with respect to an animal marked by bioluminescent compounds including reporter luciferases.

Some preferred embodiments of the present invention can be integrated with, or connected to, a CT or micro-CT scanner, as shown in FIG. 1. The bioluminescent scanning system can also be combined with other imaging systems which provide information regarding the distribution of tissue structures in vivo, in situ, or ex vivo. Alternative embodiments can serially scan an object using each modality in turn. In still further embodiments, the object can be transported between scanning modalities and one or more registration marks on the subject can be used to coordinate positions between scanning modalities. In some embodiments, information associated with x-ray CT imaging and bioluminescent imaging can be used together to estimate light scatter and/or other optical properties of tissue and thereby reconstruct a three-dimensional emission image volume registered to corresponding CT or micro-CT imaging of anatomical and pathological structures. As non-limiting examples, the system can be used to generate images of structures such as lungs and various tumors.

Some embodiments of the present invention can perform intra-organ localization of gene transcription activity with resolution capable of differentiating, for instance, gene expression in the central pulmonary airways (out to approximately the 5th-7th generation) versus parenchymal activity, and can perform localization of parenchymal activity in terms of sub-lobar regions. As a non-limiting example, the present invention can be used for small animal imaging, in particular mouse imaging. It can be used for other biomedical applications where bioluminescent signals are detectable. Some embodiments of the present invention are especially suited for small animal imaging at molecular levels. The present invention can image genetic activity in a particular organ system.

By integrating x-ray and optical imaging, optical tomography resolution can be achieved that would not be possible with a stand-alone optical system. From a corresponding x-ray CT image volume or image volume generated by other imaging energy sources, knowledge of the underlying distribution of optical scatters can be derived. This information is useful in reconstruction of images from optical data. Specifically, the present invention can directly solve for an emitting source distribution, obviating the need for reconstruction of optical properties in three dimensions. According to the present invention, the combined use of x-ray CT and BLCT transforms the nonlinear optical CT problem into a much more stable linear problem. Therefore, the present invention can significantly improve reconstruction of image data from a bioluminescent CT scanner.

One preferred embodiment according to the present invention includes a system processor that supports the desired functionality as described in detail below and a system data store (SDS) that stores data associated with this functionality such as image data and reconstruction. The system processor is in communication with the SDS.

The SDS may include multiple physical and/or logical data stores for storing the various types of information used. Data storage and retrieval functionality can be provided by either the system processor or one or more data storage processors associated with the SDS. The system processor is in communication with the SDS via any suitable

communication channel(s). The system processor may include one or more processing elements that are adapted or programmed to support the desired image storage, reconstruction and/or other functionality.

Accordingly, one preferred method of image reconstruction includes a variety of steps that may, in certain embodiments, be executed by the environment summarized above and more fully described below or be stored as computer executable instructions in and/or on any suitable combination of computer-readable media. The steps can include but are not limited to performing tomographic reconstruction of an image volume in one modality, mapping optical properties onto that volume from a database, and performing tomographic reconstruction in another modality based on the mapped optical properties.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 depicts an exemplary bioluminescent imaging device with an anatomic imaging device.

FIG. 2 depicts an exemplary single source bioluminescent CT scanner.

FIG. 3 depicts bioluminescence of the present invention viewable from multiple angles.

FIG. 4 depicts an exemplary micro-CT image of a lung showing structural components at the alveolar level.

DETAILED DESCRIPTION

One or more preferred embodiments of the invention are now described in detail hereinbelow and in the attachments hereto. Referring to the drawings, like numbers indicate like parts throughout the views. As used in the description herein and attachments hereto, the meaning of "a," "an," and "the" includes plural reference unless the context clearly dictates otherwise. Also, as used in the description herein and attachments hereto, the meaning of "in" includes "in" and "on" unless the context clearly dictates otherwise. Finally, as used in the description herein and attachments hereto, the meanings of "and" and "or" include both the conjunctive and disjunctive and may be used interchangeably unless the context clearly dictates otherwise.

Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

The present invention relates to systems and methods for detecting a light-emitting source distribution in three dimensions as well as systems and methods for reconstructing an image from the detected light signals and tomographic images obtained from one or more other modalities such as an image volume from CT or micro-CT. Some embodiments of the present invention can include one or more cameras arranged, preferably symmetrically, on a spherical surface to detect a light emitting source distribution in three dimensions. Alternative embodiments can include asymmetrical camera arrangements and/or other three-dimensional surface arrangements. In some embodiments, other optical mechanisms can be used to intercept and direct signals to the cameras including, but not limited to, mirror and/or fiber systems.

Some further embodiments can detect and record bioluminescent emissions. This image data, along with associated x-ray CT images of the same object, can be used to

reconstruct a three-dimensional emission image volume and register the bioluminescent CT image to a corresponding x-ray CT or micro-CT image volume of anatomical and pathological structures. In some such embodiments, the bioluminescent reconstruction process can be enhanced through the use of knowledge gained from x-ray CT or other anatomic information gathered by use of other imaging devices including, but not limited to, MRI or ultrasound. As a non-limiting example, emitted photons can be collected from multiple directions in three dimensions with respect to a living animal or any other light emitting structure of interest marked by bioluminescent reporter luciferases. In some embodiments, the present invention can be used to image a lung and/or various tumors.

The system and methods of the present invention differ from the diffuse CT systems and methods known in the art. Diffuse CT computes distributions of absorption and scattering coefficients from scattered light transmitted through an object. Typically, intensity-modulated light sources are used. It is well known that diffuse CT without additional knowledge will produce poor image resolution; particularly as background heterogeneity increases. However, systems and methods of the present invention assume that the optical properties of the object are already known, and then compute the photon-emitting source distribution. Therefore, the imaging models for the systems and methods of the present invention are approximately linear, while that for the prior-art diffuse CT are nonlinear and correspondingly more difficult to solve

Typical Storage and Processing Architecture

In one preferred embodiment, the imaging and reconstruction system according to the present invention includes a system processor potentially including multiple processing elements. The term processing element may refer to (1) a process running on a particular piece, or across particular pieces, of processing hardware, (2) a particular piece of processing hardware, or either (1) or (2) as the context allows. Each processing element can be supported via a standard general purpose processor such as an Intel-compatible processor platforms preferably using at least one CELERON, PENTIUM, XEON, ITANIUM (Intel Corp., Santa Clara, CA) class processor; alternative processors such as MIPS (MIPS Technologies, Mountain View, CA) or UltraSPARC (Sun

Microsystems, Palo Alto, CA) could be used in other embodiments. The system processor, or the one or more processing elements thereof, can include one or more field programmable gate arrays (FPGAs), programmable digital signal processors (DSPs) and/or application specific integrated circuits (ASICs) configured to perform at least a portion of the functionality according to the present invention. In other embodiments, an embedded microprocessor can be used such as, but not limited to, an ARM (ARM, Carlsbad, CA) processor core.

In some embodiments, the system processor can include a combination of general purpose processors, ASICs, DSPs and/or FPGAs. In some embodiments, the systems and methods of the present invention, as described above, can be distributed across multiple processing elements. In some such embodiments, aspects of the functionality or portions thereof may be executed in series or in parallel; particular functionality or portions thereof executed a multiplicity of times may also occur in series or parallel.

In a system processor including at least one general purpose processor, the general purpose processor typically runs an appropriate operating system such as WINDOWS/NT, WINDOWS 2000 or WINDOWS/XP (Microsoft, Redmond, WA), IRIX (Silicon Graphics, Mountain View, CA), SOLARIS (Sun Microsystems, Palo Alto, CA), or LINUX (or other UNIX variant). In one preferred embodiment, the Windows 2000 operating system is used.

The SDS could include a variety of primary and secondary storage elements. In one preferred embodiment, the SDS can include random access memory (RAM) as part of the primary storage; the amount of RAM might range from 512 MB to 4 GB in some embodiments. The primary storage can, in some embodiments, include other forms of memory such as cache memory, registers, non-volatile memory (e.g., FLASH, ROM, EPROM, etc.), etc.

The SDS can also include secondary storage including single, multiple and/or varied servers and storage elements. For example, the SDS can use internal storage devices connected to the system processor. In embodiments where a single processing element supports all of the system functionality, a local hard disk drive can serve as the

secondary storage of the SDS, and a disk operating system executing on such a single processing element can act as a data server receiving and servicing data requests. A system bus can serve as the communication channel between the system processor and the SDS (typically, at least RAM and the hard disk drive).

It will be understood by those skilled in the art that the different information used in the imaging and image reconstruction processes and systems according to the present invention can be logically or physically segregated within a single device serving as secondary storage for the SDS; multiple related data stores accessible through a unified management system, which together serve as the SDS; or multiple independent data stores individually accessible through disparate management systems, which may in some embodiments be collectively viewed as the SDS. The various storage elements that comprise the physical architecture of the SDS may be centrally located, or distributed across a variety of diverse locations.

The architecture of the secondary storage of the system data store may vary significantly in different embodiments. In several embodiments, database(s) are used to store and manipulate the data; in some such embodiments, one or more relational database management systems, such as DB2 (IBM, White Plains, NY), SQL Server (Microsoft, Redmond, WA), ACCESS (Microsoft, Redmond, WA), ORACLE (Oracle Corp., Redwood Shores, CA), Ingres (Computer Associates, Islandia, NY), MySQL (MySQL AB, Sweden) or Adaptive Server Enterprise (Sybase Inc., Emeryville, CA), may be used in connection with a variety of storage devices/file servers that may include one or more standard magnetic and/or optical disk drives using any appropriate interface including, without limitation, ATA, IDE and SCSI. In some embodiments, a tape library such as available from Exabyte Corporation (Boulder, CO), a storage attached network (SAN) solution such as available from EMC, Inc. (Hopkinton, MA), a network attached storage (NAS) solution such as available from Network Appliances (Sunnyvale, CA), or combinations thereof may be used. In other embodiments, the data store may use database systems with other architectures such as object-oriented, spatial, object-relational or hierarchical.

Instead of, or in addition to, those organization approaches discussed above, certain embodiments may use other storage implementations such as hash tables or flat files or combinations of such architectures. Such alternative approaches may use data servers other than database management systems such as a hash table look-up server, procedure and/or process and/or a flat file retrieval server, procedure and/or process. Further, the SDS may use a combination of any of such approaches in organizing its secondary storage architecture.

The SDS communicates with the system processor by one or more communication channels. Multiple channels can be involved in some embodiments for supporting communication between processing elements of the system processor and portions of the SDS. Such channels can include without limitation computer network, direct dial-up connection, dedicated connection, direct or indirect connection such as via a bus connection, parallel or serial connection, USB connection, null modem connection or wireless connection utilizing an appropriate communication protocol such as BLUETOOTH, IRDA, 802.11b or other suitable channel as would be known to those skilled in the art.

All forms of data, including raw, intermediate, and computed can be stored on one or more SDS either temporarily or permanently. In particular, the SDS can store, without limitation, image data, including volumetric image data, reconstruction intermediate data, final reconstructed imaging data, imaging parameters, and reconstruction parameters. Further, the SDS may, in some embodiments, store instructions for performing the various imaging and reconstruction tasks, or portions of such tasks.

Light Sensitive Cameras

In one preferred embodiment, ten CCD cameras can be arranged at the center of each identical face of a dodecahedron except for the two facing the front and back ends of an object to be imaged. Each of the 10 cameras can point to the iso-center where the object can be fixed on a transparent holder. The imaging geometry can be implemented by a structure holding each camera in a fixed position. Data from the cameras can be

transmitted to one or more processing elements for further processing and image reconstruction. A light-free housing can be used to house the imaging cameras. Once the frame of the imaging device is arranged, a camera can be mounted at any spot of the 12 nominal positions on the dodecahedron. One or more cameras can be geometrically and photographically calibrated with reference phantoms. One skilled in the art will recognize that other arrangements of cameras are possible, including geometrically symmetrical and asymmetrical. In some embodiments, one or more cameras can be rotated around an object of interest. Alternatively, or in combination, the subject of the imaging can be rotated on one or more axis. As a non-limiting example, such embodiments can be used in cases where light emission is unstable.

In one preferred embodiment, one or more cooled back-thinned integrating CCD cameras can be used for imaging. The camera package can include a 2.2L or other appropriately sized end-on liquid nitrogen dewar for cooling. Alternatively, an omni-directional dewar can be used to allow cameras to be mounted in any orientation while keeping the dewar right-side up. In some preferred embodiments, the imagers can be sensitive to one or more bioluminescent sources.

A living organism, or other structure of interest, can be scanned a using a multi-detector spiral CT, another appropriate method of imaging known to one skilled in the art, or preferably a micro x-ray CT scanner. From this imaging, a distribution of optical properties of the object can be dervied.

Camera Control

The present invention can include one or more camera control elements. A camera control element can include one or more processing elements and can be in communication with the SDS. The imaging cameras of the present invention can be in communication with the one or more camera control elements. Camera control elements can perform digitization of output from cameras and other processing as appropriate. Relevant imaging parameters can be controlled by the camera control elements. As non-limiting examples, imaging parameters such as focus, exposure time, aperture, can be

configured. Additional parameters known to one skilled in the art can also be configured as appropriate.

In some embodiments of the present invention, all cameras can be controlled by a single controller element. In other embodiments, a single controller element may be used to control multiple cameras. In such an embodiment, cameras may be arbitrarily grouped into arrays and each array can be controlled by a single controller element. Each camera acquisition chain can then operate independently. Still further embodiments can include a master controller element to provide control and synchronization for an entire camera array. In one preferred embodiment, one camera is controlled by a single controller element. One skilled in the art will recognize that other configurations of cameras and controller elements are possible.

Some embodiments can include one or more hierarchies of control elements and/or processing elements. Different levels of hierarchy can perform the same or different functions. In one preferred embodiment, images from low-level camera control elements are passed to higher level processing elements and/or control elements for additional processing and/or image reconstruction, as further described below. Control elements and processing elements can be communicatively coupled via any suitable communication means including computer network, wired or wireless direct link, bus connection and as further described below.

In one preferred embodiment, individual cameras can be controlled with an external camera control element in communication with a PCI controller card in communication with one or more processing elements. The PCI controller card and the camera control element can be communicatively coupled via an RS-422 link or other suitable serial or parallel connection. The external camera control element and the camera can be communicatively coupled via a parallel interface. In one such preferred embodiment, cameras output analog signals which are digitized by one or more external camera control elements. To minimize noise, the length of the link between the camera and the controller box can be minimized.

In one preferred embodiment, the light-emitting source data acquisition process can include one or more of the following steps: (1) reset and/or initialize cameras; (2) execute a programmable, configurable, or manual shutter open on one or more cameras; (3) execute a programmable, configurable, or manual shutter close on one or more cameras; (4) transfer image data to one or more camera control elements, processing element, or SDS; and (5) store the images in the SDS. Additional embodiments can have shutter times configured to occur simultaneously across multiple cameras and/or automatically after a predetermined time delay.

Image Reconstruction Using an Iterative Method or Other Methods

Given the ill-posed nature of the sampling geometry, the present invention can use an iterative image reconstruction approach. The iterative approach can be used in the case of incomplete and/or noisy data. Also, the iterative approach easily accommodates prior knowledge and imaging physics.

An interface from one or more camera control elements and/or processing elements to one or more reconstruction engines can be provided. The systems of the present invention can acquire optical properties of the object being imaged and then compute the light-emitting source distribution based on the optical properties. Therefore, the imaging model of the present invention is approximately linear. In one preferred embodiment, x-ray CT data is used to improve the BLCT reconstruction problem and transform it from a nonlinear one to linear one and thereby greatly stabilize it.

Even with attenuation and scattering taken into account based on a micro-CT image volume, a discrete BLCT imaging model can still be linearly expressed as $Ax = b$, where the observed data $b = (b^1, \cdots, b^M) \in R^M$, original emitting source distribution $x = (x_1, \cdots, x_M) \in R^N$, and a known non-zero $M \times N$ matrix $A = (A_{ij})$. The systems and methods of the present invention can reconstruct the image x from the data b.

A generalized BLCT algorithm according to one preferred embodiment of the present invention can include one or more of the following steps: (1) reconstruction and segmentation of an x-ray CT image volume, (2) association of optical properties of soft

and hard tissues to each segmented region in the x-ray CT volume based on a library of optical properties, (3) determination of coefficients of the forward imaging matrix $A = (A_{ij})$ based on Monte Carlo simulations, (4) reconstruction of the emitting source distribution x by inverting the matrix A, subject to the constraints imposed by the segmented anatomical structures and their properties. The systems and methods of the present invention can be used to detect and reconstruct bioluminescent emissions and well as other light-emitting source distributions in three dimensions, such as fluorescent source distributions.

As non-limiting examples, the optical properties of step two can include absorption coefficients, scattering coefficients, scattering anisotropy, indices of refraction, and other appropriate parameters known to one skilled in the art. Monte Carlo simulations can be used to predict bioluminescent signals and construct the matrix A based on the CT/micro-CT image volume of the object. After image segmentation, optical properties can be assigned to each segment based on a library of optical properties.

In one preferred embodiment both the ordered-subset expectation maximization (OS-EM) and the ordered-subset version of the simultaneous algebraic reconstruction technique (OS-SART) schemes for BLCT can be implemented. A roughness penalty method for BLCT or other method known to one skilled in the art can also be used.

Although it is our current view that an iterative method is most suitable to the image reconstruction task in one embodiment, other image reconstruction methods known to those skilled in the art can be used within the scope of the present invention. Even further, the iterative procedure we have described above is only an example, and should not not interpreted as a limiting description.

CT/Micro-CT Scanner

Any state-of-the-art micro-CT scanner can be used for the purpose of this invention. An exemplary micro-CT scanner is depicted in FIG. 1. In some preferred embodiments, the ImTek MicroCAT II

(http://www.imtekinc.com/html/microcat_ii_specifications.html) or the SkyScan-1076 in-vivo micro-CT system (http://www.skyscan.be/next/spec_1076.htm) can be used.

In other embodiments, the data acquisition system can include one or more of the following: a dedicated embedded data acquisition and control computer, two 130 kVp ultra-high resolution μfocus X-ray systems, two 100/50 mm dual-field image intensifiers, and two 2048 x 2048 CCD cameras. The scanner can include one or more processing elements in communication with the SDS, a multi-axis precision scanner and specimen manipulator with linear servo drives, remotely configurable motorized source-detector geometries, a signal and power slip ring for continuous rotation, and a means to move data between acquisition and processing. The slip ring can have two independent capacitively coupled data transmission channels with full-duplex fibre channel interfaces. The one or more processing elements, the slip ring data channels and the SDS can be communicatively coupled. In one preferred embodiment, they can be connected via one or more fiber optic cables.

One preferred embodiment of the present invention can be built on an optical grade table for vibration isolation and precision alignment. An imaging chain of source arrays, detector arrays, and accessories, alone or in combination, can be mounted on a rotating plate which is in turn supported by an open bearing and rigid stand. The axis of rotation can set to any appropriate angle including vertical and horizontal. The geometry of each imaging chain can be individually configured to suit a wide variety of operating modes. Each X-ray tube and image intensifier can be moved radially, while each image intensifier can also be moved laterally. The object can rest horizontally in a holder mounted to a linear axis with 200 mm of axial travel for slice positioning. One exemplary embodiment is capable of achieving spatial resolution of 100 lp/mm for excised samples, and temporal resolution of 1.8 seconds for objects up to 120 mm in diameter. The system can be configured to allow a wide range of intermediate combinations of scan time and spatial resolution. .

System Integration

The light-emitting source distribution CT device and the anatomic imaging scanner, such as a micro x-ray CT scanner, can be electronically and mechanically integrated but need not be in all embodiments. In one preferred embodiment, the hardware structures of the two imaging units can share a table and/or a holder attached to a table. This embodiment can allow the translation of an object for x-ray CT scanning to be extended into the light-emitting CT device in a precise and/or repeatable fashion. Some preferred embodiments of the present invention can be configured to optimize and integrate software packages for Monte Carlo simulation, BLCT reconstruction, CT and/or micro-CT data preprocessing and reconstruction, image visualization and analysis. A user interface to perform and/or to configure such functions can also be provided in some embodiments; in some such embodiments, the user interface can further allow viewing of results and may allow control of parameters with respect to such viewing. Any software capable of performing such functions can be implemented on one or more processing elements.

Exemplary Applications

The following applications are intended as illustrative examples only and are not limiting of the invention. The present invention enables lung imaging in that the structural and function information can be obtained concurrently at the molecular level, and can be evaluated on a regional, sub-lobar basis. This combination allows simultaneous examination of gene expression and anatomic structures and improves understanding of the human lungs.

The present invention can be used in gene therapy imaging, to probe the distribution of the administered gene, reporter genes such as those producing luciferase can be included in the transfecting virus. These genes cause the emission of light, enabling the functional gene to be identified within the target tissue.

Additionally, the present invention can be useful in evaluating transgene expression in the lung; gene transfer vectors; gene transfer to the respiratory epithelium of mice; in vivo bioluminescence imaging; understanding the site of transgene expression

in the lung; human lung lobe imaging and sheep-based emphysema model evaluation; understanding the site of gene therapy, and its consequences; and understanding the pathophysiology of airway vs. alveolar infection.

Throughout this application and attachments hereto, various publications may have been referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The embodiments described above are given as illustrative examples only. It will be readily appreciated by those skilled in the art that many deviations may be made from the specific embodiments disclosed in this specification without departing from the scope of the invention.

Inventors: Wang *et al.*
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FIG. 1

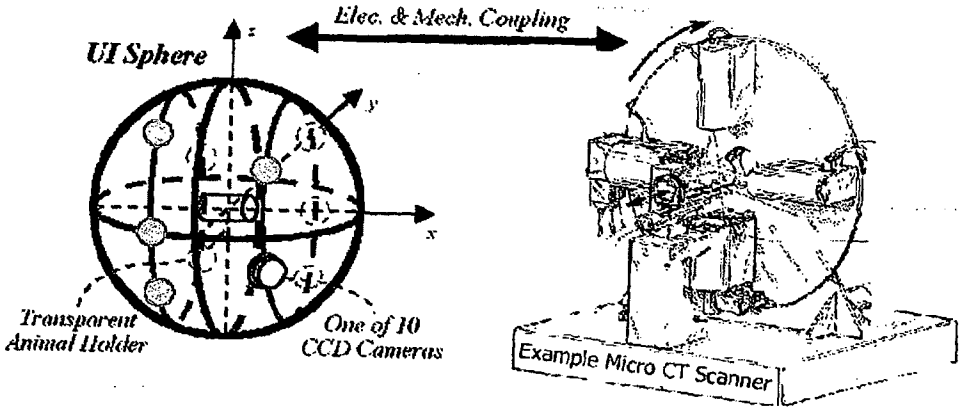

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FIG. 2

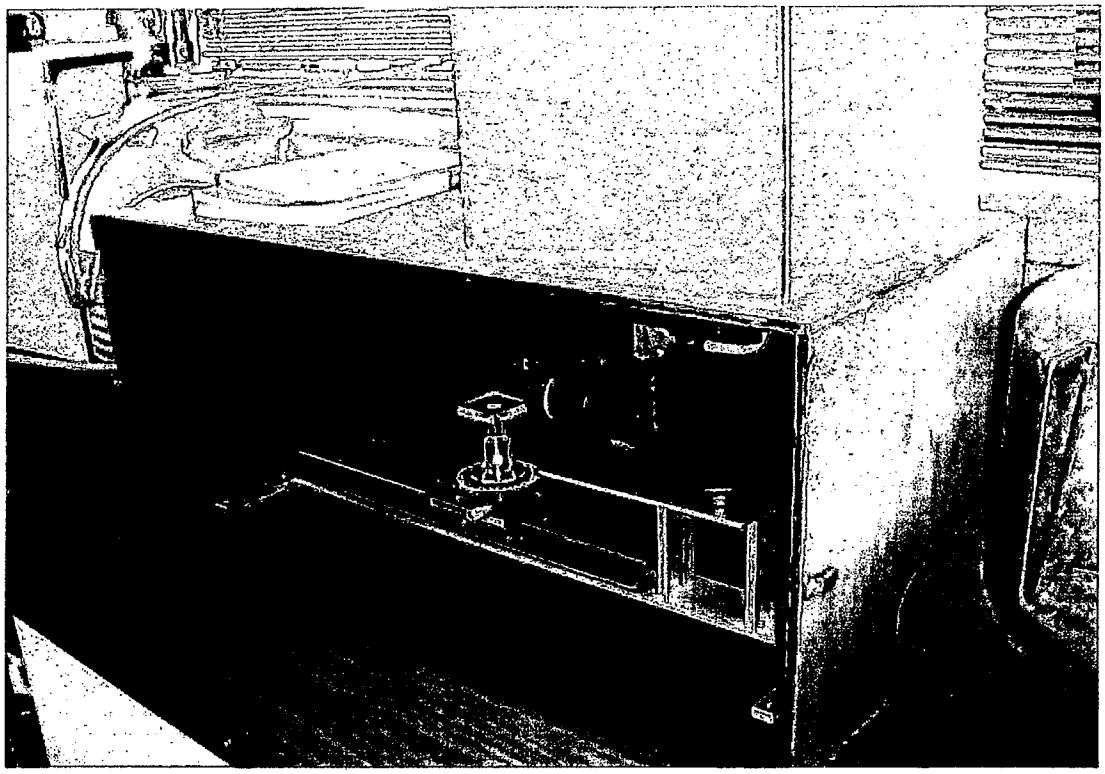

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FIG .3

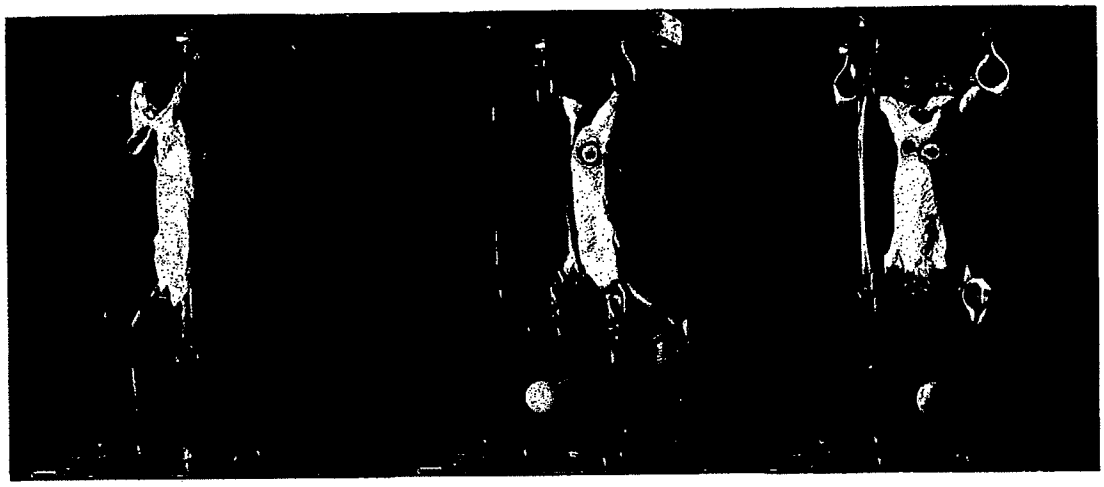

FIG. 4